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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/103,846	06/24/98	WOYCHIK R	CASE-03330

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PETER G CARROLL
MEDLEN & CARROLL
220 MONTGOMERY ST
SUITE 2200
SAN FRANCISCO CA 94104

EXAMINER
MARTIN, J

ART UNIT	PAPER NUMBER
1632	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE

Office Action Summary

Application No.	Applicant(s)
09/103,846	Woychik et al.
Examiner	**Group Art Unit**
Jill D. Martin	1632

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-28* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-28* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Claims 1-23 and 28 are generic to a plurality of disclosed patentably distinct species comprising methods involving target cells which are derived from non-human animals, plants, protist, fungi, bacteria, and viruses. Note that claims 24-27 are specifically directed to target cells that are derived from non-human animals. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Peter Carroll on September 13, 1999 a provisional election was made without traverse to prosecute the invention of methods of producing a modification in a gene of interest in non-human animal target cells, claims 1-28. Affirmation of this election must be made by applicant in replying to this Office action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any

amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claims 1-28 are pending and are under current examination, in so far as the claims are drawn to methods of producing a modification in a gene of interest in non-human animal target cells. See preceding species election.

The Information Disclosure Statement filed May 27, 1999, Paper No. 4, has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 13, 17 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods involving the use of **mouse** embryonic stem (ES) cells for the generation of a transgenic **mouse** comprising a modified gene of interest, does not reasonably provide enablement for the claimed methods involving the use of **any and all** species of embryonic stem cells for generation of **any and all** species of non-human animals comprising a modification in a first or second gene of interest. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 3 is directed to a method of producing a modification in a gene of interest in cells for generation of an organism comprising said modification in said gene of interest. Claim 13 is directed to a method of producing a modification in a gene of interest in embryonic stem cells. Claim 17 is directed to a method of producing an allelic series of modification in a gene of interest in cells for generation of an organism comprising a first or second modification in a gene of interest. Claim 27 is directed to a method of producing an allelic series of modification in a gene of interest in embryonic stem cells. Note that the terms, "cell" and "organism", are being examined only as the cell is a non-human animal cell and as the organism is a non-human animal. See species election above.

Claims 3 and 17 require that any cell (of any species of non-human animal or cell type) be manipulated to generate a non-human animal comprising a modified gene of interest. However, it is a huge leap to go from manipulation of a cell to the generation of a non-human animal such that it is unclear what Applicant intends to be encompassed within the "manipulation" of a cell, in particular it is unknown how a cell other than an embryonic stem cell would ever be capable of germline contribution since it is well known that only embryonic stem cells can contribute to germline formation of tissues and the whole animal. Further, the generation of a transgenic non-human animal generally requires much more than "manipulation of a cell", it involves essential steps such as, introducing an embryonic stem cell (having a modified gene of interest) into an

embryo, transplanting the embryo into a recipient non-human animal, allowing the embryo to develop to term, identifying a transgenic non-human animal whose genome comprises the modified gene of interest in at least one allele, and breeding the transgenic non-human animal to produce a transgenic non-human animal whose genome comprises the modified gene of interest in both alleles. The specification fails to enable the production of a transgenic animal by "manipulation of a cell" without the involvement of the essential steps above. As such, it is strongly suggested that the claims be amended to include the essential steps.

Furthermore, claims 3, 13, 17, and 27, are drawn to any non-human animal species of embryonic stem (ES) cell. However, the specification fails to enable methods involving the manipulation of embryonic stem cells for any species other than for mice. See Examples 1-3, wherein the specification teaches gene targeting in mouse embryonic stem cells. To this end, the state of the art is such that ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. (J. Mol. Med., 1997), page 214, Summary. In addition, Seamark (Reproductive Fertility and Development, 1994) reports that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Mullins et al. (Journal of Clinical Investigation, 1996) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). As the claims are drawn to methods involving the manipulation of cells for the generation of a transgenic non-human animal which

may be generated by the introduction of a transgene into an ES cell, the state of the art supports that only mouse ES cells were available for use for production of transgenics.

Accordingly, in view of the lack of guidance and direction in the specification for the isolation of true embryonic stem cells from species other than mice, the unpredictable and undeveloped state of the art for the isolation of true embryonic stem cells from species of non-human animal other than mice which contribute to germline tissue and the whole animal, as well as the claimed breadth encompassing the use of any and all species of embryonic stem cells for the generation of any and all species of non-human animal, the specification fails to enable the claimed breadth encompassing the use of any and all species of embryonic stem cells for the generation of any and all species of transgenic non-human animals. Thus, the specification as well as the state of the art supports that embryonic stem cell technology was only available for the production of transgenic mice.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 3 and 17, the recitation "manipulating cells" renders the claims vague and indefinite as to what is intended to be encompassed with regard to the generation of a non-human animal comprising a gene of interest. As such, the claims are incomplete. The only step of the method towards generation of a non-human animal is the "manipulation" of cells having a modified gene of interest. However, it is a huge leap to go from manipulation of a cell to the generation of a non-human animal such that it is unclear what Applicant intends to be encompassed within the "manipulation" of a cell. For example, the generation of a transgenic non-human animal generally requires essential steps such as, introducing an embryonic stem cell (having a modification in a gene of interest) into an embryo, transplanting the embryo into a recipient non-human animal, allowing the embryo to develop to term, identifying a transgenic non-human animal whose genome comprises the modified gene of interest in at least one allele, and breeding the transgenic non-human animal to produce a transgenic non-human animal whose genome comprises the modified gene of interest in both alleles. Note that the claims do not even require that the cell to be manipulated is an embryonic stem cell. Clarification and/or amendment to the claims is requested.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 4, 6, 7, 9-11, 13-16, 18, 20, 21, 23-25, 27, and 28 are rejected under 35 U.S.C. 102(a) as being anticipated by Thomas et al. (PNAS, 2/3/98).

Claim 1 is directed to methods including the following steps: providing a plurality of target cells capable of being cultured and an agent capable of producing at least one modification in a gene of interest in the target cell, treating the target cells with the agent under conditions such that a mixture of cells is produced, the mixture of cells having an unmodified gene of interest and a modified gene of interest, and isolating the cells having a modified gene of interest. Claim 15 is directed to a method having the same steps as claim 1, only the target cells have a first and second modification in the gene of interest. Claims 2 and 16 depend from claims 1 and 15, respectively, and are directed to the further step of comparing the modified gene of interest to the unmodified gene of interest. Claims 4 and 18 depend from claims 2 and 16, respectively, and are directed to the further step of amplifying the modified gene of interest. Claims 6, 7, 20, and 21 depend from claims 1 and 15, respectively, and are directed to a modification which is a mutation such as a deletion. Claims 9-11, 13, 23-25 and 27 are drawn to target cells that are derived from a non-human animal, a mammal, a mouse, or are embryonic stem cells. Claims 14 and 28 are drawn to different agents for producing modifications in the gene of interest.

Thomas et al. teach a method of exposing mouse ES cells to UV light and x-ray radiation. Thomas et al. report the mutation frequency for intragenic and deletion mutations at the *Hprt* locus induced by x-ray and UV treatments as compared to untreated controls. See page 1116, column 1, Results, 3rd paragraph, and Figure 1a. Thomas et al. further discuss that PCR-based analysis was consistent with Southern data for 73 of 74 of the 6-TG^r clones analyzed with an Hprt exon 7-9 specific probe. See page 1115, Materials and Methods, Mutation Analysis, column

2, and page 1116, column 2, 1st paragraph. As such, the methods of Thomas et al. meet all of the limitations of claims 1, 2, 4, 6, 7, 9-11, 13-16, 18, 20, 21, 23-25, 27, and 28.

Accordingly, Thomas et al. anticipate the claimed invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 4, 6, 8, 9-11, and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Cohen-Tannoudji et al. (Molecular and Cellular Biology, March 1998).

Claim 1 is directed to methods including the following steps: providing a plurality of target cells capable of being cultured and an agent capable of producing at least one modification in a gene of interest in the target cell, treating the target cells with the agent under conditions such that a mixture of cells is produced, the mixture of cells having an unmodified gene of interest and a modified gene of interest, and isolating the cells having a modified gene of interest. Claim 2 depends from claim 1 and is directed to the further step of comparing the modified gene of interest to the unmodified gene of interest. Claim 4 depends from claim 2 and is directed to the further step of amplifying the modified gene of interest. Claims 6 and 8 depend from claim 1 and are directed to a modification which is a strand break such as a single-strand or double-strand

break. Claims 9-11, and 13 are drawn to target cells that are derived from a non-human animal, a mammal, a mouse, or are embryonic stem cells.

Cohen-Tannoudji et al. teach a method for producing mouse ES cells with a modified allele by inducing site-specific homologous recombination via double strand breaks using an I-Sce-I restriction site. See Abstract and Figure 1, for example. Cohen-Tannoudji et al. teach amplification and Southern blot analysis to confirm the molecular nature of the recombination event at the villin gene locus. See page 1445, column 1, 4th paragraph.

Accordingly, Cohen-Tannoudji et al. anticipate claims 1, 2, 4, 6, 8, 9-11, and 13.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 9-11, 14-21, 23-25 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Marker et al. (Ref 7 of Paper No. 4).

Claim 1 is directed to methods including the following steps: providing a plurality of target cells capable of being cultured and an agent capable of producing at least one modification in a gene of interest in the target cell, treating the target cells with the agent under conditions such that a mixture of cells is produced, the mixture of cells having an unmodified gene of interest and a modified gene of interest, and isolating the cells having a modified gene of interest. Claim 15 is

directed to a method having the same steps as claim 1, only the target cells have a first and second modification in the gene of interest. Claims 2 and 16 depend from claims 1 and 15, respectively, and are directed to the further step of comparing the modified gene of interest to the unmodified gene of interest. Claims 3 and 17 depend from claims 2 and 16, respectively, and are directed to manipulating cells having the modified gene of interest to generate an organism comprising the modification. Claims 4 and 18 depend from claims 2 and 16, respectively, and are directed to the further step of amplifying the modified gene of interest. Claims 5 and 19 are drawn to the further step of sequencing the amplified modified gene of interest. Claims 6, 7, 20, and 21 depend from claims claim 1 and 15, respectively, and are directed to a modification which is a mutation such as a deletion or a single base substitution. Claims 9-11, and 23-25 are drawn to target cells that are derived from a non-human animal, a mammal, or a mouse. Claims 14 and 28 are drawn to different agents for producing modifications in the gene of interest.

Marker et al. teach mutagenesis experiments using the mouse specific-locus test. Marker et al. teach the examination of 24 chemical- and radiation-induced mutations at the *short ear* locus. See Table 1. Marker et al. report that 8 of the 11 mutations induced by ENU consisted of single base substitutions. See page 437, column 1, 1st paragraph. Marker et al. further report that PCR and Sequence analysis were carried out for characterization of the mutant strains as compared to the corresponding genomic region of *Bmp5* from wild-type mice. See page 437, column 1, 3rd paragraph. **Note** that, as written, the claims read on both *in vitro* and *in vivo* mutagenesis since the claims do not require that the target cells are isolated, but only "capable of

being cultured." Furthermore, note that claims 3 and 17 are indefinite (see rejection under 112, 2nd paragraph) and, thus, considered to be made obvious by the methods of *in vivo* mutagenesis. Thus, the method of mutagenesis of Marker et al. meets all of the limitations of the methods of claims 1-7, 9-11, 14-21, 23-25 and 28.

Accordingly, Marker et al. anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 9, 12, 15, 23, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marker et al. taken with Schulte-Merker et al. (Ref 24 of Paper No. 4).

Claim 1 is directed to methods including the following steps: providing a plurality of target cells capable of being cultured and an agent capable of producing at least one modification in a gene of interest in the target cell, treating the target cells with the agent under conditions such that a mixture of cells is produced, the mixture of cells having an unmodified gene of interest and a modified gene of interest, and isolating the cells having a modified gene of interest. Claim 15 is directed to a method having the same steps as claim 1, only the target cells have a first and second modification in the gene of interest. Claims 9 and 23 are drawn to target cells that are derived from a non-human animal. Claims 12 and 26 are drawn to non-human animal target cells that are zebrafish cells.

Marker et al. teach mutagenesis experiments using the mouse specific-locus test. Marker et al. teach the examination of 24 chemical- and radiation-induced mutations at the *short ear* locus. See Table 1. Marker et al. report that 8 of the 11 mutations induced by ENU consisted of single base substitutions. See page 437, column 1, 1st paragraph. Marker et al. differ from the claimed invention in that they do not specifically teach mutagenesis in cells of the zebrafish. However, at the time the claimed invention was made, Schulte-Merker et al. point out that the zebrafish combine the advantages of the amphibian and the mammalian system, and that, as in mice, genetic analysis in zebrafish is possible. Schulte-Merker et al. also point out that screens for mutations affecting early embryonic development have led to the isolation of a number of valuable mutants. See page 1022, column 2, 2nd paragraph. Further, Schulte-Merker et al. teach

characterization of the zebrafish homolog of the mouse T gene and, thus, demonstrate that molecular mechanisms present in fish and mammals may be very similar.

Accordingly, in view of the teachings of Schulte-Merker et al., it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the mutagenesis methods of Marker et al. by substituting the zebrafish system for the mouse system with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to perform mutagenesis experiments in the zebrafish system because the zebrafish combines advantages of both amphibian and mammalian systems, and particularly since the zebrafish exhibit some level of conservation in many mammalian genes such as the mouse T gene.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6, 8, 15, 20, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marker et al. taken with Slamenova et al. (Mutation Research, 1997).

Claim 1 is directed to methods including the following steps: providing a plurality of target cells capable of being cultured and an agent capable of producing at least one modification in a gene of interest in the target cell, treating the target cells with the agent under conditions such that a mixture of cells is produced, the mixture of cells having an unmodified gene of interest and a modified gene of interest, and isolating the cells having a modified gene of interest. Claim 15 is directed to a method having the same steps as claim 1, only the target cells have a first and second modification in the gene of interest. Claims 6 and 20 depend from claim 1 and 15, respectively, and are directed to a modification which is a strand break. Claims 8 and 22 depend from claims 6 and 20, respectively, and are directed to a stand break which is a single or double strand break.

Marker et al. teach mutagenesis experiments using the mouse specific-locus test. Marker et al. teach the examination of 24 chemical- and radiation-induced mutations at the *short ear* locus. See Table 1. Marker et al. report that 8 of the 11 mutations induced by ENU consisted of single base substitutions. See page 437, column 1, 1st paragraph. Marker et al. differ from the claimed invention in that they do not specifically teach mutagenesis involving DNA strand breaks. However, at the time the claimed invention was made, Slamenova et al. teach the examination of

the level of single strand breaks of DNA in different mammalian cell lines damaged by MNNG (N-methyl-N'-nitro-N-nitrosoguanidine. See page 247, column 1, 1st paragraph, for example.

Accordingly, in view of the teachings of Slamenova et al., it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made to modify their mutagenesis experiments by using the mutagen, MNNG, for induction of DNA breaks with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to use MNNG to induce DNA breaks for study of DNA rejoining in mammalian cells as undertaken by Slamenova et al., for example.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

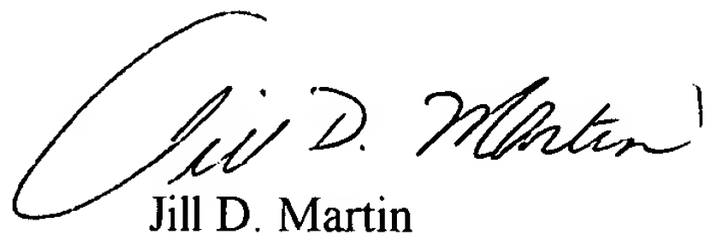
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jill Martin whose telephone number is (703)305-2147.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, can be reached at (703)308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-0196.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.



Jill D. Martin

Patent Examiner